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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/197,056	11/20/98	RUSSELL S	3789/77553

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EXAMINER	
WILSON,M	

ART UNIT	PAPER NUMBER
1633	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/197,056	RUSSELL ET AL.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8,9,13,14,16 and 18-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8,9,13,14,16 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's arguments filed 6-22-01, paper number 17, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 4, 7, 11, 12, 15 and 17 have been canceled. Claims 19 and 20 have been added. Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18-20 are under consideration in the instant application.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in the United Kingdom on 9-6-97 and 11-7-97 (9718872.6 and 9723448.8). It is noted, however, that applicant has not filed a certified copy of the applications as required by 35 U.S.C. 119(b).

Specification

1. The description of Fig. 2 should begin "Figures 2A and 2B" (page 7, line 12).

Claim Objections

2. Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18-20 are objected to because of the following informalities: the preamble of claims 1, 14 and 19 should read "encoding an immunogenic

polypeptide" to reflect the "said immunogenic polypeptide" in the body of the claim. Appropriate correction is required.

The marked up copy of claim 18 is incorrect. The phrase "comprising transforming the isolated leukocyte..." has been changed to "comprising introducing into the leukocyte...". The marked up copy of claim 18 does not reflect this change. Applicants are reminded that the marked up copy is to reflect all changes made to the claims.

Claim Rejections - 35 USC § 112

3. Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18 remain rejected and claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating the expression of a nucleic acid sequence encoding a protein *in vitro* comprising a) transfecting a cell with a nucleic acid sequence encoding a protein operably linked to a tetracycline regulatable promoter and b) regulating the expression of the sequence by altering the tetracycline concentration to which the cell is exposed such that expression of the protein is altered and a method of regulating expression of a nucleic acid sequence encoding a protein in a transgenic mouse comprising a) transfecting a mouse ES cell with a nucleic acid sequence encoding a protein operably linked to a tetracycline regulatable promoter and a nucleic acid encoding a tet regulatory protein operably linked to a promoter, b) introducing the transfected ES cells into pseudopregnant mouse such that transgenic mice whose genomes comprise said nucleic acid sequences such that the protein able to be functionally expressed in the mice to detectable

levels and c) regulating the expression of the protein by altering the tetracycline concentration to which the transgenic mice are exposed such that expression of the protein is altered, does not reasonably provide enablement for using the method to treat or prevent disease, using any protein, any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The claims as written encompass broad and divergent technologies, i.e. methods of regulating protein expression in transgenic animals, methods of regulating protein expression in cells administered to a mammal for the purpose of therapy and methods of regulating marker protein expression in cells administered to a mammal for the purpose of monitoring the cells, et al. The methods include transfecting cells *in vitro* or *in vivo*, using therapeutic proteins or marker proteins, regulating protein expression *in vitro* or *in vivo*, administering cells to mammals that have had an immune response to a protein. Because of the divergent technologies encompassed by the claims, the lack of clarity in the claims (especially regarding the essential steps of the method) (see 112/2nd) and the art rejections, the following enablement rejection is based on the examiners best guess as to what applicants consider their invention.

All of the claims still encompass therapeutic embodiments because the claims recite using any protein or "immunogenic proteins" which are defined as therapeutic proteins (page 7, line 24) and claims 1-3, 5, 6, 8, 9 and 13 require the host has an immune response prior to administering the cell. Applicants have not provided any arguments regarding how to use the method or cells

claimed to obtain a therapeutic effect. Therefore, therapeutic embodiments of the claims remain rejected for reasons of record because the specification does not teach how to use the method or cells to obtain a therapeutic effect.

Applicants argue the method can be used to study regulation of marker proteins *in vivo* (page 6-8). Applicants argument is not persuasive. Claims 1, 14 and 19 require "immunogenic polypeptides" which are defined as proteins that induce a therapeutic immune response (page 7, line 24). Claim 18 encompasses using any protein. None of the claims are limited to marker proteins. Claim 1 may require that the mammal has an immune response to the protein prior to administering cells expressing the protein. The specification and the art at the time of filing did not teach using such a mammal to study marker gene expression. Limiting the claims to marker proteins may overcome this rejection; however, clarification of how such a method correlates to mammals that already have an immune response against the marker protein would be required.

Applicants argue the method could be used to express TCR molecules to study the T-cell activation process (page 32, lines 17-18). Applicants argument is not persuasive because such a method would require exposing a mammal to an immunogenic antigen followed by administering a cell expressing a TCR which is not encompassed by claims 1-3, 5, 6, 8, 9 and 13. Instead claims 1-3, 5, 6, 8, 9 and 13 require that the immune response is directed toward an immunogenic polypeptide that is the same as the immunogenic polypeptide encoded by the vector. Furthermore, a TCR is not an "immunogenic polypeptide" because it does not induce an immune response - the antigen does. Finally, the specification does not provide adequate guidance

regarding how to use a leukocyte encoding a TCR to study the T-cell activation process. Specifically, it is unclear when to regulate expression of the TCR in the host. Therefore, the specification does not enable the methods claim for the purpose of studying T-cell activation.

Applicants argue that all that remains to satisfy enablement is to administer the cells to a mammal that has already made an immune response to the protein (page 8, first full para.). Applicants argument is not persuasive. The specification and the art did not teach the host had already made an immune response to the protein prior to receiving the cells. Page 22, lines 5-12 suggest such an approach; however, such a suggestion is not adequate to enable the method. The specification does not provide adequate guidance when the host must have circulating antibodies, immunocompetent memory cells or any other immune response or how to use such a host after administering the cell. The specification does not teach what effect administering the cell has on a host that has already had an immune response to the protein. The only disclosed purpose for administering a cell expressing a protein to a mammal after the mammal has already had an immune response to the immunogenic polypeptide is to treat cancer (page 3, line 21). However, the state of the art of gene therapy was unpredictable for reasons of record. The specification does not teach the protein, level of expression, target tissue, mode of delivery or immune response obtained required to have a therapeutic effect. The specification does not teach the parameters required to use the method claimed in a mammal that has previously made an immune response to the protein such that a therapeutic effect is obtained. The methods also relate to making a transgenic mammal; however, the specification does not teach transfecting an ES cell

with a vector encoding an immunogenic protein and transferring the ES cell into a mammal that has had an immune response to the immunogenic protein. The methods also relate to regulating marker protein expression in a mammal; however, the specification does not teach transferring a cell to a mammal that has had an immune response to a marker protein. Therefore, the mere suggestion of using the method in a mammal that has already been exposed to the polypeptide is not adequate to enable the method.

Claims 1-3, 5, 6, 8, 9, 13 and 18 remain rejected and claims 19-20 are rejected because the specification does not teach how to transfect cells *in vivo* for reasons of record (page 7, 6 lines from the bottom of previous office action). Such embodiments do not appear to be a part of applicants invention and have not been addressed in applicants arguments. To expedite prosecution, please amend claims 1, 18 and 19 to transfecting the cells *in vitro.*

Applicants argue the purpose of the method is not to induce an immune response but to produce an immunogenic polypeptide *in vivo* despite the immune response (Page 10, 2nd full para.). The argument is unclear. Why would one want to produce an immunogenic polypeptide (defined as a therapeutic protein) in a host despite the fact that the host has already made an immune response to the immunogenic polypeptide? The only readily apparent purpose is for therapy which is discussed above. If the argument is referring to producing TCR in a host to study T-cell activation, applicants argument is not persuasive because the claims require that the immune response is against the TCR which does not have a disclosed use that is enabled. If the immune response is not against the TCR, it is unclear what immune response is required to study

T-cell activation of cells expressing TCR or how to regulate TCR expression to study T-cell activation.

Applicants argue that the introduction of genes to cells using viral vectors is well known in the art (claim 13). Applicants argue that the methods do not call for the introduction of sequence into cells *in vivo* or regulating the expression of the protein *in vivo* (page 11, 2nd para.). Applicants arguments are not persuasive. The claims are not limited to transfecting cells *in vitro* or regulating the protein expression *in vitro*. Furthermore, the specification does not teach the parameters required to administering cells transfected with viral vectors encoding a protein such that the protein is functionally expressed *in vivo*. Nor are such teachings provided in the art at the time of filing. As such, the mere suggestion of using a viral vector in the method is not adequate to enable using a viral vector in the method claimed.

4. Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18 remain rejected and claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18-20 are indefinite because the phrase "mammal that has made an immune response to said immunogenic polypeptide" is unclear. It is unclear if the mammal has been exposed to the immunogenic polypeptide prior to the "introducing" step or if the mammal has made an immune response to "said immunogenic polypeptide" which is encoded by the vector. As stated previously, it is unclear if the mammal has been previously

exposed to the immunogenic polypeptide or if applicants are attempting to claim the immune response obtained by introducing a vector encoding the immunogenic polypeptide. Prior exposure to the immunogenic polypeptide is not required in the claim.

Claims 1-3, 5, 6, 8, 9, 13 and 18 remain indefinite and claims 19 and 20 are indefinite because the claims 1, 18 and 19 are directed to "regulating the expression of a nucleic acid sequence" but only results in expression of a nucleic acid sequence. Applicants argue the phrase "as permitted in the presence or absence of tetracycline or an analog thereof" is descriptive of regulation. Applicants argument is not persuasive because the phrase is not a clear, positive step indicating that expression of the protein is altered in the presence or absence of tetracycline.

Claims 1-3, 5, 6, 8, 9, 13, 14, 16 and 18 remain indefinite and claims 19 and 20 are indefinite are indefinite because the phrase "altering the concentration of tetracycline...to which the cells [leukocyte] is exposed" is indefinite as it relates to the step of administering the cells. In particular, it is unclear how the phrase is used in new claim 19 in relation to inhibiting protein expression *in vitro* - it cannot be determined when the concentration of tet is altered in relationship to when protein expression is inhibited *in vitro*. Applicants argue that the ground of rejection are improper because any situation is encompassed by the claim. Applicants argument is not persuasive. Overall, the claims do not clearly recite when the mammal is first exposed to the immunogenic polypeptide, when the immunogenic polypeptide encoded by the vector is expressed, when tet is first administered, when tet concentration is altered, or when expression of the immunogenic polypeptide is altered. Specifically, it cannot be determined whether when tet is

administered and when the tet concentration is altered in relationship to the first and second exposures to the immunogenic polypeptide. Therefore, the metes and bounds of the order in which the method steps are performed cannot be determined. Clarification is required.

Claim Rejections - 35 USC § 102

5. Claim 1 remains rejected and claims 18 as newly amended and claim 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Shockett (Shockett et al, July 1995, PNAS, USA, Vol. 92, pages 6522-6526) for reasons of record.

Shockett taught transducing fertilized eggs with a vector encoding luciferase under the control of the tet operator (page 6523, Fig. 1 and Fig. 1 legend; page 6525, paragraph bridging columns 1 and 2). The eggs were implanted into a pseudopregnant female which is considered equivalent to introducing a cell into a mammal as claimed. Tetracycline was removed which is equivalent to "altering the concentration of tetracycline" as claimed. Luciferase is an immunogenic polypeptide because it is a non-mammalian protein that is recognized by the immune system of mammals as foreign. Applicants argue that Shockett does not teach that the mammal had made an immune response to luciferase prior to introducing the cell into the mammal. Applicants argument is not persuasive. The claim encompasses introducing a cell into a mammal and obtaining an immune response after the cell is introduced. The phrase "introducing, into a mammal that has made an immune response to said immunogenic polypeptide, a cell..." is not limited to introducing a cell comprising a vector encoding an immunogenic polypeptide into a

mammal that has made an immune response to said immunogenic polypeptide prior to introducing the cell because the cell may become the mammal that has an immune response, because the claim does not state the immune response occurs prior to administering the cell to the mammal, because it is unclear if the immune response is a result of exposure to the immunogenic polypeptide encoded by the vector and because it is unclear if "said immunogenic polypeptide" refers to a polypeptide to which the mammal has been exposed prior to introducing the cell (see 112/2nd). Shockett introduces the vector into egg cells which become the mammal that inherently makes an immune response to luciferase which is encompassed by the claim.

Claim 18 as newly amended requires regulating expression of a coding sequence in a leukocyte by introducing DNA encoding a protein operatively linked to a tet operator and DNA encoding a tet-sensitive DNA-binding expression-regulating protein into the leukocytes. Claim 19 requires the coding sequence is an "immunogenic polypeptide." Shockett taught transducing fertilized eggs with a vector encoding luciferase operably linked to the tet operator and a vector encoding tTAk which is a "tetracycline-sensitive DNA-binding expression-regulating polypeptide" operably linked to the tet operator (page 6523, Fig. 1 and Fig. 1 legend; page 6525, paragraph bridging columns 1 and 2). The eggs were cultured in the presence of 0.5 μg/ml tetracycline (page 6523, col. 1, last full para.) which is equivalent to inhibiting expression *in vitro*. Claim 18 is anticipated by Shockett by introducing DNA encoding luciferase operably linked to the tet operator and DNA encoding tTAk which is a tet-sensitive DNA-binding expression-regulating protein into all the cells of a transgenic mouse. Removing tet from the mouses' diet induced

luciferase expression in the spleen and thymus which equivalent to regulating expression in the leukocytes. Luciferase is an immunogenic polypeptide because it is a non-mammalian protein that is recognized by the immune system of mammals as foreign. The eggs were implanted into a pseudopregnant female which is equivalent to transferring cells into a mammal as claimed. Therefore, Shockett anticipates the claim as written.

6. Claims 14 and 16 remain rejected under 35 U.S.C. 102(b) as being anticipated by Hoffmann (Hoffmann et al., PNAS, USA, May 1996, Vol. 93, pages 5185-5190) for reasons of record.

Hoffmann taught transfecting lymphocytes with a retroviral vector encoding LacZ operatively linked to the tet operator and also encoding the tetR-VP16 (page 5186, column 2, 2nd paragraph; page 5187, column 1, first full paragraph, line 90; page 5189, col. 1, last line). LacZ is an immunogenic polypeptide because it is a bacterial protein that is recognized by mammals as foreign. The lymphocytes taught by Hoffmann are "leukocytes" as claimed. The media used to culture the cells in Hoffmann is a physiologically acceptable diluent. Hoffmann taught LacZ expression is controlled by altering the concentration of tet to which the leukocyte is exposed. The claim is directed toward the leukocyte and does not require expression of the protein or controlling expression of the protein; therefore, the claim does not distinguish the structure or function of the leukocyte from that taught by Hoffmann. The cells of Hoffmann are equivalent to the cells claimed because they have the same nucleic acids and because protein expression may controlled by altering the concentration of tetracycline. The phrase "after introduction to a

mammal" is an intended use and does not bear patentable weight on the claim because it may not occur. Therefore, Hoffmann anticipates the claims.

Applicants argue that Hoffmann only taught transfecting myoblasts which are muscle cell progenitors and not leukocytes as claimed. Applicants argument is not persuasive. As cited previously, page 5187, col. 1, first full paragraph, line 90 and page 5189, col. 1, last line of Hoffmann clearly taught transfecting lymphocytes which is all that is required in the claim.

Claim Rejections - 35 USC § 103

7. Claim 18 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffmann (Hoffmann et al., PNAS, USA, May 1996, Vol. 93, pages 5185-5190) for reasons of record.

Hoffmann taught transfecting lymphocytes with a retroviral vector encoding LacZ operatively linked to the tet operator and also encoding the tetR-VP16 (page 5186, column 2, 2nd paragraph; page 5187, column 1, first full paragraph, line 90; page 5189, col. 1, last line). Lymphocytes are considered leukocytes. TetR-VP16 is considered a "tetracycline-sensitive DNA-binding expression-regulating polypeptide" because it is binds DNA and regulate LacZ expression according to the level of tetracycline present. Hoffmann did not expressly teach altering the concentration of tet thereby regulating the expression of the polypeptide in lymphocytes as newly amended. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the concentration of tet thereby regulating the expression of LacZ in the lymphocytes because Hoffmann taught altering the concentration of tet

thereby regulating expression of LacZ in myoblasts transfected with the vector encoding LacZ operably linked to a tet-regulatable promoter (page 5187, col. 1, para. 2 and 3). The purpose of transfecting the cells with a vector encoding a protein operably linked to a tet-regulatable promoter as taught by Hoffmann is to regulate expression of the protein. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to alter the concentration of tet in lymphocytes to regulate the expression of LacZ in the lymphocytes.

Claims 2 and 3 appear to be free of the prior art of record because the prior art of record did not teach or suggest administering a leukocyte comprising a nucleic acid sequence encoding an immunogenic polypeptide operably linked to a tet-regulatable promoter into a mammal and altering the concentration of tet to which the leukocyte is exposed so as to achieve expression of said the polypeptide in the mammal. Claims 5 and 6 appear to be free of the prior art of record because the prior art of record does not teach or suggest introducing a cell expressing a immunogenic polypeptide as claimed into a mammal wherein the mammal has an immune response to the polypeptide prior to administering the cell. Claims 8, 9 and 20 appear to be free of the prior art of record because the prior art of record does not teach or suggest reaching a maximum level of polypeptide expression after 2 days or inducing expression after 2 days by administering tetracycline as claimed. Claim 13 appears to be free of the prior art of record because the prior art of record did not teach or suggest administering a cell comprising a viral

vector encoding an immunogenic polypeptide operably linked to a tet-regulatable promoter into a mammal as claimed so as to achieve expression of said polypeptide in the mammal.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER